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Donor Lymphocyte Infusion for Relapsed Hematological Malignancies after Allogeneic Hematopoietic Cell Transplantation: Prognostic Relevance of the Initial CD3⁺ T Cell Dose

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Abstract

The impact of donor lymphocyte infusion (DLI) initial cell dose on its outcome is known in patients with chronic myeloid leukemia but limited in patients with other hematological malignancies. In this retrospective study, we evaluated the effect of initial DLI CD3⁺ cell dose on graft-versus-host disease (GVHD) and overall survival after DLI given for relapse of any hematological malignancies after allogeneic hematopoietic cell transplantation (HCT) with high- or reduced-intensity conditioning. The cohort included 225 patients. Initial DLI CD3⁺ cell dose per kilogram of recipient body weight was $\leq 1 \times 10^7$ (n = 84; group A), >1.0 to $<10 \times 10^7$ (n = 58; group B), and $\geq 10 \times 10^7$ (n = 66; group C). The initial cell dose was unknown for the remaining 17 patients. Cumulative incidence rates of GVHD at 12 months after DLI were 21%, 45%, and 55% for groups A, B, and C, respectively. Multivariate analysis showed that initial DLI CD3⁺ cell $\geq 10 \times 10^7$ dose per kilogram is associated with an increased risk of GVHD after DLI ($P = .03$). Moreover, an initial DLI CD3⁺ cell dose of 10×10^7 or higher did not decrease the risk of relapse and did not improve overall survival. Thus, these results support the use of less than 10×10^7 CD3⁺ cell per kilogram as the initial cell dose of DLI for treatment of persistent or recurrent hematological malignancy after HCT.

Introduction

Allogeneic hematopoietic cell transplantation (HCT) has the potential to provide long-term survival and even cure in patients with hematological malignancies 1 and 2. Nonetheless, relapse of malignancy after HCT remains a major cause of transplantation failure. Donor lymphocyte infusion (DLI) is one approach frequently used to treat patients with relapse of hematologic malignancy after allogeneic HCT. The DLI effect is mediated through the immunologic antitumor activity of donor T cells and possibly natural killer cells 3, 4, 5 and 6. Since the first report of DLI in patients with relapsed chronic myeloid leukemia (CML) after allogeneic HCT by Kolb et al. in 1990 [6], DLI has become a common approach to treat not only CML but also acute leukemia, lymphoma, myelodysplastic syndrome (MDS), and multiple myeloma (MM) that have relapsed after allogeneic HCT 7, 8, 9, 10, 11, 12 and 13. The beneficial graft-versus-leukemia effect of DLI may be offset by morbidity and mortality related to graft-versus-host disease (GVHD). Although a low initial cell dose followed by escalation of doses of DLI can minimize the risk of GVHD in patients treated for relapsed CML 14, 15 and 16, the data regarding the impact of initial cell dose on outcomes after DLI for other relapsed hematological malignancies are limited. The primary objective of the current study was to determine the effect of the initial DLI CD3⁺ T cell dose on subsequent GVHD requiring systemic treatment and on overall survival (OS) after DLI.

Patients and Methods

The study cohort included 225 patients treated with DLI for relapsed hematological malignancies after allogeneic HCT from November 1993 through October 2011. Patients received high- or reduced-intensity conditioning regimens before HCT according to standard treatment plan or prospective clinical trials and were treated at the Fred Hutchinson Cancer Research Center (n = 212) and at 3 participant institutions in the Seattle Nonmyeloablative HCT Consortium: the University of Torino (n = 9), the Puget Sound VA Health Care System (n = 2), and the Medical

College of Wisconsin (n = 2). Follow-up was complete through July 2012. All patients provided informed consent for treatment according to transplantation protocols approved by each institutional review board. In addition, separate institutional approval was obtained to gather data from patient records and databases retrospectively.

DLI

All 225 patients in this study received DLI for treatment of relapsed hematological malignancies after HCT. No prophylactic DLI treatment was given. One hundred fifty-four patients were treated with DLI in prospective clinical trials, and 71 patients received DLI as a treatment plan. Patients with rapidly progressive malignancies (ie, acute myeloid or lymphoid leukemia, CML in blast phase, high-grade MDS, intermediate-high grade non-Hodgkin lymphoma, Hodgkin lymphoma, or aggressive multiple myeloma) received chemotherapy or radiation before DLI according to specific protocols or at the discretion of the attending physician. Treatment with tyrosine kinase inhibitor or interferon was generally discontinued before DLI. Patients were eligible to receive DLI if they were not receiving systemic treatment for GVHD, had no evidence of active GVHD at the time of DLI, and had evidence of donor chimerism. No immunosuppressive agents were given after DLI to prevent GVHD. Among 128 patients with available information regarding the DLI product, 32 patients received a granulocyte-colony stimulating factor (G-CSF) mobilized product for DLI. Twelve patients received IL-2 after DLI as part of a prospective clinical trial, as previously described [17].

GVHD Definition

DLI-related GVHD was defined as any acute GVHD [18] or chronic GVHD (NIH criteria or historical criteria) 19 and 20 after DLI that required systemic treatment. As clinically acute and chronic GVHD occurring after DLI have overlapping onset times 21 and 22, for the purpose of evaluating the incidence of GVHD after DLI, we defined DLI-related GVHD as any GVHD after DLI (acute or chronic) that required systemic treatment. Serious GVHD after DLI was evaluated according to previously reported criteria [23].

Statistical Methods

Overall survival after DLI was estimated by the Kaplan-Meier method. Cumulative incidence of relapse and GVHD after DLI were estimated by standard methods, treating death as a competing risk. Cox regression was used to evaluate risk factors for GVHD, OS, and relapse and disease progression after DLI. Risk factors evaluated in univariate analysis for each of the outcomes (GVHD, OS, and relapse or disease progression after DLI) included initial DLI CD3⁺ cell dose, patient age at DLI, donor-recipient gender, diagnosis at time of DLI, disease status at time of DLI, donor origin, donor-recipient HLA match, graft stem cell source, conditioning intensity, acute and chronic GVHD before DLI, interval between HCT to DLI, cytoreductive treatment before DLI, donor blood CD3 and whole marrow chimerism at the time of DLI, lymphocyte count at the time of DLI, use of G-CSF-mobilized product for DLI, use of IL-2 after DLI, and year of DLI. Multivariate models included all factors significant at the .05 level in univariate analysis for each outcome, as well as age and the factors most significantly disparate among the cell dose groups (donor origin, conditioning intensity, and year of DLI). In analyzing the impact of subsequent DLI on overall survival, the second DLI was treated as a time-dependent covariate in a Cox regression model. Comparisons of CD3⁺ cell dose between the initial and second DLI was by paired *t*-test.

Results

Patient Characteristics

A total of 225 patients underwent treatment with DLI for persistent or relapse hematological malignancies after HCT including CML (n = 56), acute myeloid leukemia (AML) (n = 71), MDS (n = 22), acute lymphoblastic leukemia (ALL) (n = 21), MM (n = 23), lymphoma (n = 21), chronic lymphocytic leukemia (CLL)/lymphoma (n = 8), myelofibrosis (n = 2), and myeloproliferative disorder (n = 1). Patients were classified into one of the following risk categories: (1) high-risk myeloid malignancies group that included patients with AML, MDS, CML (blast crisis [BC], accelerated phase [AP]), myelofibrosis, and myeloproliferative disorder, (n = 111); (2) high-risk lymphoid malignancies group that included patients with ALL and high-grade lymphomas (Hodgkin lymphoma, diffuse large B cell lymphoma, transformed non-Hodgkin lymphoma), (n = 37); (3) low-risk lymphoid malignancies group that included patients with CLL, MM, other lymphomas, (n = 36); and (4) those with CML-chronic phase (CP) (n = 41).

The median age of the 225 patient cohort was 46 years (range, 3 to 74), and 59% (n = 132) were male. Patients received transplantations from HLA-matched related (n = 171) or unrelated (n = 41) donors. Thirteen patients had HLA-mismatched donors, and 58 patients (26%) received reduced-intensity conditioning regimens before HCT. The median time interval from HCT to relapse was 11.3 months (range, 1 to 180); from HCT to DLI, 15.5 months (range, 21.1 to 215). One hundred forty-four patients (64%) received cytoreductive therapy before DLI, and 55 patients (24%) had achieved complete remission at the time of DLI. The initial DLI CD3⁺ cell dose per kilogram was $\leq 1 \times 10^7$ in 84 patients (group A), >1.0 to $<10 \times 10^7$ in 58 patients (group B), and $\geq 10 \times 10^7$ in 66 patients (group C). The remaining 17 patients received an unknown initial dose. Median follow-up after DLI was 78 months (range, .1 to 197). Characteristics of the cohort according to the initial DLI CD3⁺ cell dose administered are shown in Table 1.

Table 1.

Patient Characteristics

Characteristic	CD3 ⁺ Cell Dose, per Kilogram				P Value
	Unknown (n = 17)	Group A $\leq 10^7$ (n = 84)	Group B $>10^7$ to $<10^8$ (n = 58)	Group C $\geq 10^8$ (n = 66)	
Patient age at DLI					.14
0-29 yr	4	12 (14)	13 (22)	9 (14)	
30-44 yr	7	25 (30)	11 (19)	27 (41)	
45-59 yr	5	29 (35)	25 (43)	22 (33)	
60-74 yr	1	18 (21)	9 (16)	8 (12)	
Donor-recipient gender (n = 220)					.17
Other	14	65 (82)	40 (69)	52 (79)	
Female to male	3	14 (18)	18 (31)	14 (21)	
Disease diagnosis/risk at time of DLI					.36
CML-chronic phase	6	16 (19)	9 (16)	10 (15)	
Low-risk lymphoid malignancies [†]	0	20 (24)	6 (10)	10 (15)	
High-risk myeloid malignancies [‡]	6	36 (43)	32 (55)	37 (56)	
High-risk lymphoid malignancies [§]	5	12 (14)	11 (19)	9 (14)	

CD3⁺ Cell Dose, per Kilogram

Characteristic	Unknown (n = 17)	Group A ≤10⁷ (n = 84)	Group B >10⁷ to <10⁸ (n = 58)	Group C ≥10⁸ (n = 66)	P Value *
Disease status at time of DLI					.05
Complete remission	2	14 (17)	19 (33)	20 (30)	
Not in complete remission	15	70 (83)	39 (67)	46 (70)	
Donor origin					<.0001
Related	13	48 (57)	46 (79)	64 (97)	
Unrelated	4	36 (43)	12 (21)	2 (3)	
Donor-recipient HLA match					.07
Matched	13	77 (92)	57 (98)	65 (98)	
Mismatched	4	7 (8)	1 (2)	1 (2)	
Graft stem cell source (n = 201)					.004
Bone marrow	12	31 (49)	21 (38)	45 (68)	
Mobilized blood	5	32 (51)	34 (62)	21 (32)	
Conditioning intensity					<.0001
Myeloablative	16	47 (56)	41 (71)	63 (95)	
Nonmyeloablative	1	37 (44)	17 (29)	3 (5)	
Prior acute GVHD (n = 218)					.05
0-I	4	34 (44)	25 (43)	17 (26)	
II-IV	13	43 (56)	33 (57)	49 (74)	
Prior chronic GVHD					.14
No	11	60 (71)	39 (67)	37 (56)	
Yes	6	24 (29)	19 (33)	29 (44)	
Time from HCT to DLI					.50
>1 yr	11	51 (61)	31 (53)	42 (64)	
≤1 yr	6	33 (39)	27 (47)	24 (36)	
Cytoreduction before DLI (n = 220)					.02
No	6	37 (45)	18 (31)	15 (24)	
Yes	11	45 (55)	40 (69)	48 (76)	
Donor CD3 chimerism at time of DLI (n = 91)					.70
>95%	1	32 (70)	20 (71)	7 (58)	
≤95%	4	14 (30)	8 (29)	5 (42)	
Donor BM chimerism at time of DLI (n = 114)					.75
>95%	5	25 (54)	18 (60)	13 (50)	
≤95%	7	21 (46)	12 (40)	13 (50)	
Lymphocyte count at time of DLI (n = 217)					.01

CD3⁺ Cell Dose, per Kilogram

Characteristic	Unknown (n = 17)	Group A ≤10 ⁷ (n = 84)	Group B >10 ⁷ to <10 ⁸ (n = 58)	Group C ≥10 ⁸ (n = 66)	P Value *
≥10 ³ /μL	10	47 (61)	24 (42)	25 (38)	
<10 ³ /μL	7	30 (39)	33 (58)	41 (62)	
G-CSF mobilized product for DLI (n = 128)					.02
No	0	41 (84)	37 (79)	18 (56)	
Yes	0	8 (16)	10 (21)	14 (44)	
IL-2 after DLI					.02
No	15	83 (99)	55 (95)	58 (88)	
Yes	2	1 (1)	3 (5)	8 (12)	
Year of DLI					<.0001
1992-1996	6	5 (6)	8 (14)	23 (35)	
1997-2001	6	26 (31)	14 (24)	33 (50)	
2002-2006	2	30 (36)	27 (47)	10 (15)	
2007-2011	3	23 (27)	9 (16)	0	

DLI indicates donor lymphocyte infusion; CML, chronic myeloid leukemia; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; BM, bone marrow; G-CSF, granulocyte-colony stimulating factor.

Data are presented as n (%) unless otherwise indicated.

*

Among groups A, B, and C.

†

Includes chronic lymphocytic leukemia/lymphoma, multiple myeloma, lymphomas not high grade.

‡

Includes acute myeloid leukemia, myelodysplastic syndrome, chronic myeloid leukemia (blast crisis, accelerated phase), myelofibrosis, myeloproliferative disorders.

§

Includes acute lymphoblastic leukemia, high-grade lymphomas (Hodgkin lymphoma, diffuse large B cell lymphoma, transformed non-Hodgkin lymphoma).

GVHD after DLI

Of the 225 treated patients, 86 (39%) developed GVHD that required systemic therapy after DLI, and 29 of 86 cases had serious GVHD as previously defined [23]. The median interval from DLI to GVHD that required systemic treatment was 39 days (range, 6 to 1029). The incidence rates of GVHD at 12 months after DLI according to initial cell dose were 21%, 45%, and 55% for groups A, B, and C, respectively (Figure 1A).

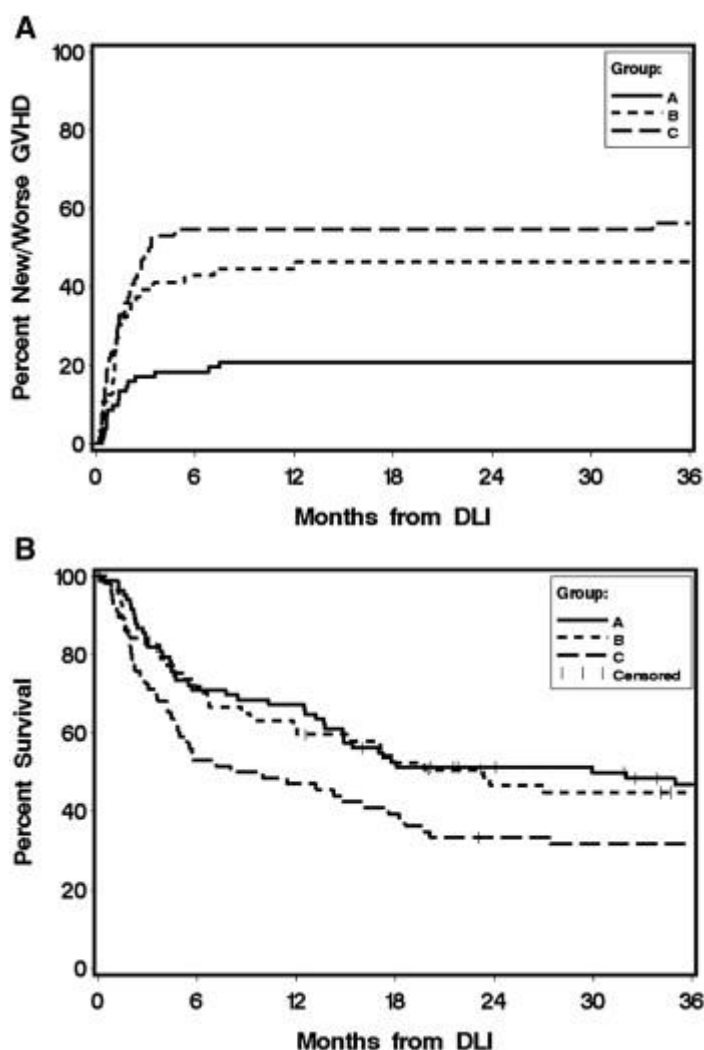


Figure 1.

Outcome after donor lymphocyte infusion (DLI) according to initial DLI cell dose. (A) Shows cumulative incidence of graft-versus-host disease after DLI according to initial CD3⁺ cell dose. Twelve-month cumulative incidence of GVHD for initial DLI cell dose group A ($\leq 1 \times 10^7$ CD3⁺ cell/kg) was 21%, compared with 45% ($P = .01$) for initial cell dose group B ($>1 \times 10^7$ to $<10 \times 10^7$ CD3⁺ cell/kg) and 55% ($P < .0001$) for initial cell dose group C ($\geq 10 \times 10^7$ CD3⁺ cell/kg). (B) Shows overall survival after DLI according to initial CD3⁺ cell dose. Three-year overall survival rates were 47% for cell dose group A, 45% ($P = .16$) for cell dose group B, and 32% for cell dose group C ($P = .01$).

Results of univariate and multivariate analysis of risk factors for the development of GVHD after DLI are shown in Table 2. In the multivariate analysis, 2 factors showed a statistically significant association with increased risk of GVHD after DLI: (1) initial DLI CD3⁺ cell dose $\geq 10 \times 10^7$ /kg (hazard ratio [HR], 2.4; 95% CI, 1.1 to 5.4; $P = .03$), and (2) short interval between transplantation to DLI of 1 year or less (HR, 2.95; 95% CI, 1.7 to 5.2; $P = .0002$) (Table 2). In univariate analysis, higher initial CD3⁺ cell dose was associated with an increased risk for serious GVHD after DLI for group B (HR, 4.34; 95% CI, 1.4 to 13.6; $P = .01$) and for group C (HR, 4.80; 95% CI, 1.6 to 14.7; $P = .006$) compared to group A. Because of the small number of patients experiencing serious GVHD, multivariate analysis was not performed. Although DLI given in more recent years was associated with a decreased risk of GVHD in the univariate analysis, this factor did not reach statistical significance in the multivariate analysis. A history of acute or chronic GVHD before DLI or donor type was not statistically significantly associated with increased risk of GVHD after DLI (Table 2).

Table 2.
Risk Factors Analysis for GVHD after DLI

	Univariate		Multivariate (n = 194)	
	HR (95% CI)	P Value	HR (95% CI)	P Value
CD3 ⁺ cell dose				
≤10 ⁷ cells/kg	1.0		1.0	
>10 ⁷ to <10 ⁸ cells/kg	2.74 (1.5-5.0)	.001	1.82 (.9-3.7)	.10
≥10 ⁸ cells/kg	3.87 (2.2-6.9)	<.0001	2.40 (1.1-5.4)	.03
Patient age at DLI				
0-29 yr	1.0		1.0	
30-44 yr	1.06 (.6-2.0)	.86	.82 (.4-1.8)	.62
45-59 yr	1.26 (.7-2.3)	.46	1.35 (.6-2.8)	.42
60-74 yr	.45 (.2-1.1)	.09	.55 (.2-1.8)	.32
Donor-recipient gender				
Other	1.0			
Female to male	1.26 (.8-2.1)	.37		
Disease diagnosis/risk at time of DLI				
CML-chronic phase	1.0		1.0	
Low-risk lymphoid malignancies*	.94 (.4-2.3)	.89	1.04 (.3-3.8)	.95
High-risk myeloid malignancies [†]	2.53 (1.3-4.8)	.005	1.72 (.6-4.8)	.30
High-risk lymphoid malignancies [‡]	1.65 (.7-3.7)	.23	1.41 (.4-4.7)	.58
Disease status at time of DLI				
Complete remission	1.0		1.0	
Not in complete remission	.61 (.4-1.0)	.03	.99 (.5-1.8)	.97
Donor origin				
Related	1.0		1.0	
Unrelated	.76 (.5-1.3)	.29	.99 (.5-2.0)	.97
Donor-recipient HLA match				
Matched	1.0			
Mismatched	1.10 (.4-2.7)	.84		
Graft stem cell source				
Bone marrow	1.0			
Mobilized blood	1.04 (.7-1.6)	.86		
Conditioning intensity				
Myeloablative	1.0		1.0	
Nonmyeloablative	.57 (.3-1.0)	.04	.71 (.3-1.6)	.42
Prior acute GVHD (n = 218)				
0-I	1.0			
II-IV	1.32 (.8-2.1)	.23		
Prior chronic GVHD				
No	1.0			

	Univariate		Multivariate (n = 194)	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Yes	1.24 (.8-1.9)	.34		
Time from HCT to DLI				
>1 yr	1.0		1.0	
≤1 yr	2.57 (1.7-3.9)	<.0001	2.95 (1.7-5.2)	.0002
Cytoreduction before DLI				
No	1.0		1.0	
Yes	1.88 (1.2-3.1)	.01	1.32 (.6-2.9)	.48
Donor CD3 chimerism at time of DLI				
>95%	1.0			
≤95%	1.87 (.8-4.1)	.12		
Donor BM chimerism at time of DLI				
>95%	1.0			
≤95%	1.26 (.7-2.3)	.46		
Lymphocyte count at time of DLI				
≥10 ³ /μL	1.0		1.0	
<10 ³ /μL	2.13 (1.4-3.3)	.0008	1.41 (.8-2.3)	.19
G-CSF mobilized product for DLI				
No	1.0			
Yes	.95 (.5-1.8)	.87		
IL-2 after DLI				
No	1.0			
Yes	1.22 (.6-2.6)	.62		
Year of DLI				
1992-1996	1.0		1.0	
1997-2001	.77 (.4-1.3)	.34	.93 (.5-1.8)	.83
2002-2006	.57 (.3-1.0)	.05	.67 (.3-1.3)	.25
2007-2011	.21 (.1-.6)	.002	.33 (.1-1.1)	.07

DLI indicates donor lymphocyte infusion; HR, hazard ratio; CML, chronic myeloid leukemia; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; BM, bone marrow; G-CSF, granulocyte-colony stimulating factor.

*

Includes chronic lymphocytic leukemia/lymphoma, multiple myeloma, lymphomas not high grade.

†

Includes acute myeloid leukemia, myelodysplastic syndrome, chronic myeloid leukemia (blast crisis, accelerated phase), myelofibrosis, myeloproliferative disorders.

‡

Includes acute lymphoblastic leukemia, high-grade lymphomas (Hodgkin lymphoma, diffuse large B cell lymphoma, transformed non-Hodgkin lymphoma).

Overall Survival after DLI

The overall survival rates at 3 years according to initial DLI cell dose were 47%, 45%, and 32% for groups A, B, and C, respectively (Figure 1B). At the time of analysis, 71 patients (31%) were alive after DLI. Survivors were 28 of 41 patients (68%) treated for CML-CP, 3 of 15 patients (20%) treated for CML-AP/BC, 15 of 71 patients (21%) for AML, 4 of 21 patients (19%) for ALL, 1 of 22 patients (4%) for MDS, 7 of 23 patients (30%) for MM, 2 of 8 patients (25%) for CLL, and 8 of 21 patients (38%) treated for lymphomas, 2 of 2 patients with myelofibrosis, and 1 patient with myeloproliferative disorder.

As demonstrated in Table 1, we found no statistically significant imbalance in the distribution of diagnosis risk groups between the 3 initial DLI CD3⁺ cell dose groups ($P = .36$). Because of the small number of patients in each of the initial DLI cell dose groups in the different diagnostic risk groups (ie, CML-CP, low-risk lymphoid, low-risk myeloid, and high-risk lymphoid malignancies), these 4 diagnostic risk groups were combined into 2 risk categories for the analysis of OS according to the initial DLI CD3⁺ cell dose, as follows: (1) low-risk disease, including CML-CP, CLL, MM, low-grade lymphomas and (2) high-risk disease, including myeloid malignancies (AML, MDS, CML-AP/BC), myelofibrosis, myeloproliferative disorder, and high-risk lymphoid malignancies (ALL, high-grade lymphomas [Hodgkin lymphoma, diffuse large B cell lymphoma, transformed non-Hodgkin lymphoma]). Figure 2 shows the univariate analysis of OS after DLI according to the initial CD3⁺ cell dose and the 2 diagnosis risk categories. The 3-year OS for the low-risk category was 73% for group A, 53% for group B, and 55% for group C ($P = .07$) (Figure 2A). The 3-year OS for the high-risk category was 27% for group A, 42% for group B, and 22% for group C, but the difference in OS between the 3 cell doses was not statistically significant ($P = .35$) (Figure 2B).

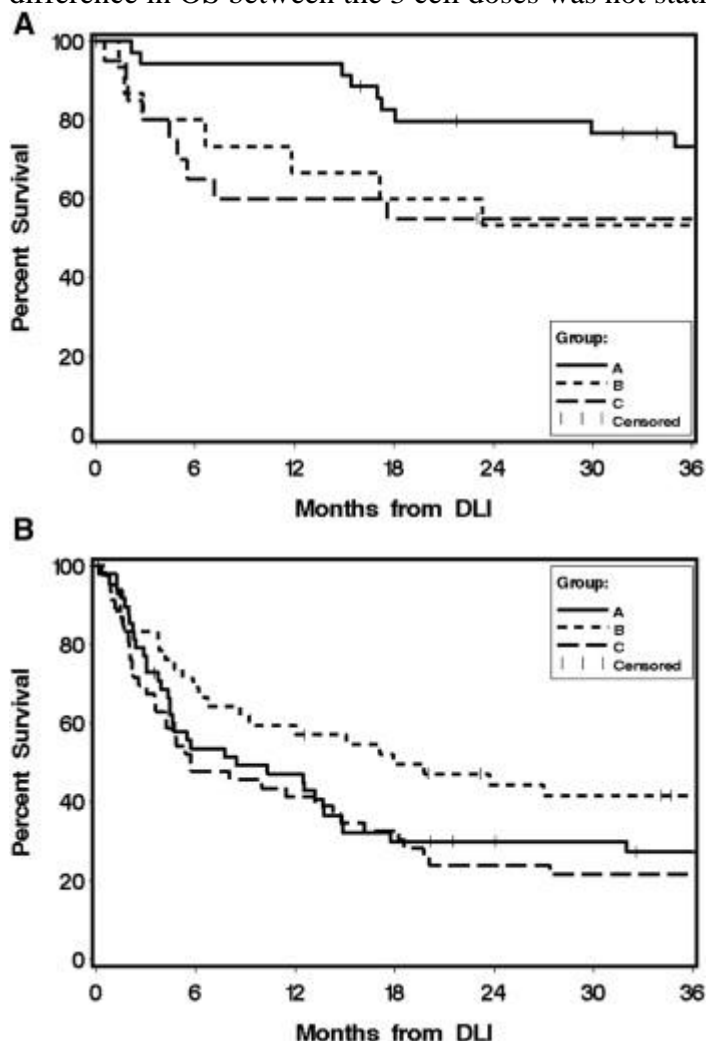


Figure 2.

Overall survival after donor lymphocyte infusion (DLI) according to initial CD3⁺ cell dose and disease risk category. (A) Shows the overall survival for the low-risk category. One- and 3-year overall survival were 94% and 73% for cell dose A, 67% and 53% for cell dose B, and 60% and 55% for cell dose C ($P = .07$). Low-risk category included chronic myeloid leukemia-chronic phase and chronic lymphocytic leukemia, multiple myeloma, and low-risk lymphomas. (B) Shows the overall survival for the high-risk category. One- and 3-year overall survival were 47% and 27% for cell dose group A, 60% and 42% for cell dose group B, and 41% and 22% for cell dose group C ($P = .35$). High-risk category included high-risk myeloid malignancies (acute myeloid leukemia, myelodysplastic syndrome, chronic myeloid leukemia [blast crisis, accelerated phase], myelofibrosis, myeloproliferative disorders, and high-risk lymphoid malignancies [acute lymphoblastic leukemia, high-grade lymphomas [Hodgkin lymphoma, diffuse large B cell lymphoma, transformed non-Hodgkin lymphoma]).

Univariate analysis of OS according to the initial CD3⁺ cell dose for specific diagnosis such as CML and other disease categories is shown in Supplemental Figure 1. For patients treated with DLI for relapsed CML, 3-year OS according to the initial DLI cell dose was 81% for group A, 46% for group B, and 50% for group C, but these differences did not reach statistical significance ($P = .07$) (Supplemental Figure 1A). For patients given DLI for relapsed lymphoma, CLL, and MM, the 1- and 3-year OS were 85% and 43%, respectively, for patients given cell dose A; 91% and 64%, respectively for patients treated with cell dose B; and 46% and 31%, respectively, for cell dose C. These differences were not statistically significant ($P = .25$) (Supplemental Figure 1B). No association between initial DLI CD3⁺ cell dose and OS was noted for patients treated for relapsed AML or MDS with 3-year OS of 32%, 40%, and 28% for initial DLI CD3⁺ cell doses A, B and C, respectively ($P = .99$) (Supplemental Figure 1C).

Results of multivariate analysis for risk factors for mortality after DLI are presented in Table 3. Three factors were statistically significantly associated with an increased risk of mortality after DLI: (1) DLI within 1 year after HCT (HR, 2.66; 95% CI, 1.7 to 4.2; $P < .0001$); (2) age 60 or older (HR, 2.69; 95% CI, 1.1 to 6.3; $P = .02$); and (3) high-risk lymphoid malignancies (HR, 2.62; 95% CI, 1.0 to 6.8; $P = .05$). As shown in Table 2, a trend for an association between high-risk myeloid malignancies and an increased mortality risk was noted ($P = .06$). More recent DLI was associated with decreased risk for mortality, with an HR of .27 (95% CI, .1 to .6; $P = .002$) for patients treated with DLI between 2007 to 2011 compared with patients treated between 1992 to 1996. Initial DLI cell dose did not affect mortality either for the entire cohort (Table 3) or for the cohort of patients with diseases other than CML-CP (group B: HR, .88; $P = .61$; group C: HR, 1.22; $P = .51$).

Table 3.

Risk Factor Analysis for Overall Mortality after DLI

	Univariate		Multivariate (n = 181)	
	HR (95% CI)	P Value	HR (95% CI)	P Value
CD3 ⁺ cell dose				
≤10 ⁷ cells/kg	1.0		1.0	
>10 ⁷ to <10 ⁸ cells/kg	1.35 (.9-2.0)	.16	.98 (.6-1.7)	.93
≥10 ⁸ cells/kg	1.64 (1.1-2.4)	.01	1.25 (.7-2.3)	.48
Patient age at DLI				
0-29 yr	1.0		1.0	
30-44 yr	.99 (.6-1.6)	.95	1.02 (.6-1.9)	.95
45-59 yr	1.02 (.6-1.6)	.94	1.44 (.8-2.7)	.25
60-74 yr	1.42 (.8-2.4)	.20	2.69 (1.1-6.3)	.02

	Univariate		Multivariate (n = 181)	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Donor-recipient gender				
Other	1.0			
Female to male	1.19 (.8-1.7)	.38		
Disease diagnosis/risk at time of DLI				
CML-chronic phase	1.0		1.0	
Low-risk lymphoid malignancies*	2.93 (1.5-5.8)	.002	1.47 (.5-4.2)	.48
High-risk myeloid malignancies [†]	5.05 (2.8-9.1)	<.0001	2.29 (1.0-5.4)	.06
High-risk lymphoid malignancies [‡]	4.64 (2.4-9.0)	<.0001	2.62 (1.0-6.8)	.05
Disease status at time of DLI				
Complete remission	1.0			
Not in complete remission	1.18 (.8-1.7)	.39		
Donor origin				
Related	1.0		1.0	
Unrelated	.86 (.6-1.3)	.44	1.05 (.6-1.8)	.87
Donor-recipient HLA match				
Matched	1.0			
Mismatched	1.14 (.6-2.2)	.70		
Graft stem cell source				
Bone marrow	1.0		1.0	
Mobilized blood	1.72 (1.2-2.4)	.002	1.42 (.8-2.5)	.22
Conditioning intensity				
Myeloablative	1.0		1.0	
Nonmyeloablative	1.24 (.9-1.8)	.24	0.75 (.4-1.6)	.46
Prior acute GVHD (n = 218)				
0-I	1.0			
II-IV	1.07 (.8-1.5)	.68		
Prior chronic GVHD				
No	1.0			
Yes	.98 (.7-1.4)	.89		
Time from HCT to DLI				
>1 yr	1.0		1.0	
≤1 yr	3.04 (2.2-4.2)	<.0001	2.66 (1.7-4.2)	<.0001
Cytoreduction before DLI				
No	1.0		1.0	
Yes	2.35 (1.6-3.4)	<.0001	1.37 (.7-2.5)	.31
Donor CD3 chimerism at time of DLI				
>95%	1.0			
≤95%	1.39 (.8-2.4)	.25		
Donor BM chimerism at time of DLI				

	Univariate		Multivariate (n = 181)	
	HR (95% CI)	P Value	HR (95% CI)	P Value
>95%	1.0			
≤95%	2.08 (1.3-3.3)	.003		
Lymphocyte count at time of DLI				
≥10 ³ /μL	1.0		1.0	
<10 ³ /μL	1.72 (1.2-2.4)	.001	1.16 (.8-1.8)	.50
G-CSF mobilized product for DLI				
No	1.0			
Yes	1.06 (.7-1.7)	.81		
IL-2 after DLI				
No	1.0			
Yes	1.41 (.8-2.5)	.23		
Year of DLI				
1992-1996	1.0		1.0	
1997-2001	.89 (.6-1.4)	.59	.65 (.4-1.1)	.10
2002-2006	.79 (.5-1.2)	.30	.46 (.2-.9)	.02
2007-2011	.58 (.3-1.1)	.09	.27 (.1-.6)	.002

DLI indicates donor lymphocyte infusion; HR, hazard ratio; CML, chronic myeloid leukemia; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; BM, bone marrow; G-CSF, granulocyte-colony stimulating factor.

*

Includes chronic lymphocytic leukemia/lymphoma, multiple myeloma, lymphomas not high grade.

†

Includes acute myeloid leukemia, myelodysplastic syndrome, chronic myeloid leukemia (blast crisis, accelerated phase), myelofibrosis, myeloproliferative disorders.

‡

Includes acute lymphoblastic leukemia, high-grade lymphomas (Hodgkin lymphoma, diffuse large B cell lymphoma, transformed non-Hodgkin lymphoma).

Of the 225 patients, 46 received 2 DLIs, 13 patients received 3 DLIs, and 1 patient received 4 DLIs. A time-dependent Cox regression analysis showed no significant effect of subsequent DLIs on OS (HR, .95; 95% CI, .6 to 1.4, *P* = .82).

Causes of Death

A total of 154 patients have died. Deaths occurred in 49 of 84 patients (58%) in cell group A, in 41 of 58 patients (71%) in cell dose group B, and in 55 of 66 patients (83%) in cell group C. The most common cause of death after DLI was progressive disease or relapse of malignancy in all 3 cell dose groups: 90% of deaths in group A, 73% of deaths in group B, and 67% of deaths in group C. GVHD was the primary cause of death in 4 patients (8%) in group A, 3 patients (7%) in group B, and 5 patients (9%) in group C. Table 4 summarizes the cause of death according to the initial DLI cell dose groups.

Table 4.

Cause of Death According to Initial DLI CD3 Cell per Kilogram Dose Groups

	Group A (n = 49)	Group B (n = 41)	Group C (n = 55)
GVHD	4 (8%)	3 (7%)	5 (9%)
Relapse or progressive disease	44 (90%)	30 (73%)	37 (67%)
Relapse or progressive disease and GVHD	0	3 (7%)	4 (7%)
Other cause death	0	3 (7%)	4 (7%)
Unknown cause of death	1 (2%)	2 (5%)	5 (9%)

GVHD indicates graft-versus-host disease.

Data are presented as n (%) unless otherwise indicated. $P = .32$ (excluding unknown causes)

Relapse and Disease Progression after DLI

Among the 225 patients, 166 (74%) had relapse and/or progressive disease after DLI. Results of univariate and multivariate analysis for relapse and/or progressive disease after DLI are shown in Supplemental Table 1. Three factors statistically significantly affected the risk of relapse or disease progression after DLI in the multivariate analysis: (1) interval of 1 year or less from HCT to DLI (HR, 1.92; 95% CI, 1.3 to 2.9; $P = .002$); (2) age of 60 and older (HR, 2.33; 95% CI, 1.1 to -5.1 ; $P = .03$); and (3) initial CD3⁺ cell dose of $>1 \times 10^7$ to $<10 \times 10^7$ /kg compared with lower cell dose (HR, .54; 95% CI, .3 to $-.9$; $P = .01$). Initial CD3⁺ cell dose of $\geq 10 \times 10^7$ /kg was not associated with decreased relapse rate. Analysis for risk of relapse according to the initial DLI CD3⁺ cell dose among patients with diseases other than CML-CP showed similar results. The intermediate cell dose was associated with a decreased relapse rate (HR, .57; 95% CI, .4 to .9; $P = .02$), but the highest cell dose was not.

Aplasia after DLI

Aplasia after DLI was evaluated in 154 patients who participated in prospective DLI studies for relapsed hematological malignancies after HCT. Fifteen of 154 (9.7%) patients developed aplasia after DLI. Five of 15 patients received an initial DLI dose of $\geq 10 \times 10^7$ CD3⁺/kg, 2 patients received a dose of 9×10^7 CD3⁺/kg, 1 patient received a dose of 2.5×10^7 CD3⁺/kg, and the rest of the patients received a dose of 1×10^7 CD3⁺/kg.

Discussion

DLI is an attractive salvage treatment option for patients with persistent or relapsed hematological malignancies after high- or reduced-intensity HCT 7, 8, 9, 10 and 11. Previous studies have suggested optimal initial total nucleated cells and lymphocyte doses of DLI associated with a low risk of GVHD and mortality and yet maintenance of the desirable graft-versus-malignancy effect for treatment of relapsed CML after allogeneic HCT 14, 15 and 16. Limited data are available on the impact of DLI CD3⁺ cell dose on GVHD and mortality after DLI in patients treated for other hematological malignancies, however, and the appropriate initial cell dose of DLI for treatment of recurrent non-CML hematological malignancies after HCT remained unsettled. Thus, the primary objective of our study was to determine the effect of the initial DLI cell dose on GVHD and OS after DLI in patients treated for any hematological malignancies that relapsed after allogeneic HCT. DLI contains a variety of cell types, and the response to DLI could be mediated by several mechanisms. T lymphocytes have significant effects on both graft-versus-leukemia and GVHD because of their longevity after transfusion in vivo and their ability to target minor histocompatibility antigens shared between leukemic and normal host tissue as well as antigens unique to leukemia cells 24, 25 and 26. Therefore, we focused our analysis on the effect of the initial CD3⁺ T cell dose on GVHD and survival after DLI. This retrospective analysis of 225

patients confirms that adoptive immunotherapy with donor lymphocytes may be an effective treatment for patients with hematological malignancies who experience relapse after allogeneic HCT, and the results suggest that the initial CD3⁺ cell dose may influence the outcome independently of other relevant factors.

Our multivariate analysis suggests that the risk for developing GVHD after DLI significantly increases with CD3⁺ cell dose $\geq 10 \times 10^7$ /kg, regardless of diagnosis, pre-DLI acute or chronic GVHD, or interval between HCT and DLI. GVHD, a pathological process initiated by the activation of donor T cell after adoptive transfer into the allogeneic recipient [27], has been a major direct complication after DLI [7, 17, 24, 28, 29, 30, 31, 32, 33 and 34]. Earlier reports demonstrated that the dose of allogeneic total nucleated cells and lymphocytes infused for DLI is a risk factor of GVHD after DLI in patients with relapsed CML [14, 21 and 30]. Chalendon et al. showed that $>1 \times 10^7$ CD3⁺ cells/kg was correlated with a higher frequency of GVHD after DLI in patients with relapsed CML after HCT [21]. In our study, initial DLI CD3⁺ cell dose of $\geq 10 \times 10^7$ /kg was associated with a 2.4-fold increase in the risk of GVHD after DLI compared with cell doses $\leq 1.0 \times 10^7$ in patients treated for any hematological malignancy that relapsed or progressed after allogeneic HCT after either high-intensity or reduced-intensity conditioning. Initial DLI CD3⁺ cell dose of $>1.0 \times 10^7$ to $<10 \times 10^7$ /kg was not associated with an increased risk for GVHD compared to a lower cell dose.

We then sought to determine the effect of the initial CD3⁺ cell dose on OS after DLI. Earlier studies evaluated the effect of DLI mononuclear cells or T cell dose for the treatment of CML [14 and 15]. Guglielmi et al. demonstrated that for the treatment of relapsed CML, an initial DLI cell dose of $\leq 20 \times 10^8$ mononuclear cells/kg was associated with less GVHD and better survival than higher mononuclear cell doses [14]. Similar to the findings by Guglielmi et al., we demonstrated better OS for patients with relapsed CML who were treated with lower initial DLI CD3⁺ cell dose. Although our association did not reach statistical significance, likely because of the small cohort, our and earlier results demonstrate that for patients with CML, initial CD3⁺ cell dose of 1×10^7 or lower has survival advantage as compared to higher CD3⁺ cell dose. In contrast to the association between initial DLI CD3⁺ cell dose and OS in CML, we did not demonstrate such an association for patients with AML or MDS. Earlier analyses to evaluate the correlation between cell dose and response rate in AML showed that increasing the cell dose beyond 1.5×10^8 T cell/kg did not add to the response rate [35]. A study by Choi et al., however, appeared to show a better response rate with a higher dose of T cells [36]. In our study, we demonstrated 3-year overall survival of 32%, 40%, and 28% for patients with relapsed AML or MDS treated with $\leq 1 \times 10^7$ CD3⁺ cells/kg, 1.1 to 9.9×10^7 CD3⁺ cells/kg, and $\geq 10 \times 10^7$ CD3⁺ cells/kg, respectively ($P = .99$). Although these results do not demonstrate correlation between initial DLI CD3⁺ cell dose and OS, they do show that initial DLI CD3⁺ cell dose $\geq 10 \times 10^7$ /kg does not provide survival benefit. Therefore, considering that an initial DLI cell dose of $\geq 10 \times 10^7$ CD3⁺ cells/kg is associated with an increased risk of GVHD after DLI, our results suggest that initial CD3⁺ cell doses $\geq 10 \times 10^7$ /kg should be avoided. Although we found no statically significant difference between initial cell dose groups and OS, patients in the low-risk disease category might achieve better survival with a lower DLI cell dose (Figure 2A). Our evaluation of the relationship between CD3⁺ cell dose and OS for lymphoma, CLL, and MM showed an association between the initial DLI CD3⁺ cell dose and OS; however, this association did not reach statistical significance (Supplemental Figure 1B). The number of ALL patients in our cohort was too small to derive significant conclusions.

Relapse or progressive disease was the main cause of death after DLI at all 3 cell dose groups, with no statistically significant decrease in the proportion of patients who died because of relapse among patients who were treated with higher CD3⁺ cell doses.

We then evaluated the association between initial DLI cell dose and relapse or disease progression after DLI. Our data demonstrate a decreased risk of relapse and/or disease progression with initial DLI CD3⁺ dose of $>1 \times 10^7$ to $<10 \times 10^7$ but not with higher cell dose. The results were not different when CML-CP patients were excluded from the analysis. Similar observations have been

made previously in ALL patients treated with DLI [35]. Although no conclusive statement can be made because of the small numbers, the lower response rates with higher CD3⁺ cell dose could reflect higher numbers of infused T regulatory cells, which might dampen the graft-versus-tumor effect.

This study has several limitations. The data were mostly collected retrospectively, the patient population is heterogeneous, patients were treated according to a variety of protocols with different treatment strategies, and methods and timing of follow-up were not standardized. Additionally, better supportive care has improved the survival of patients who were treated in more recent years compared with patients who were treated earlier. Despite those limitations, we believe that this study gives a reliable estimate of the effect of initial CD3⁺ cell dose on GVHD and survival after DLI for treatment of relapsed hematological malignancies after HCT.

Our results demonstrate that an initial DLI CD3⁺ cell dose per kilogram $\geq 10 \times 10^7$ is associated with increased risks of GVHD after DLI, without improving survival. These findings are clinically relevant, because they support a recommendation to infuse less than 10×10^7 CD3⁺ cell/kg as the initial cell dose of DLI for treatment of recurrent hematological malignancy, including non-CML after allogeneic HCT.

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